REMARKS

Claims 1-15 are pending. Claims 1-10 and 12-15 were rejected in the Office Action. Claim 11 was objected to for a reason not elaborated. Applicants presume claim 11 was objected to because the disclosure was objected to for an informality, addressed below.

Preliminarily, Applicants wish to thank the Office for the rejoinder of claims 8 and 9. Applicants also acknowledge, with appreciation, the withdrawal of all the rejections under 35 USC §112, first and second paragraphs.

The disclosure was objected to because of the typographical error on page 6, line 2 of the specification -- "bridie" should be "bridge." Applicants have corrected the typographical error, as well as another one on the same line. Applicants expect that this objection with be withdrawn and claim 11 will be allowed.

Rejections Under 35 U.S.C. § 102(e)/103

Claims 1-10, 12-13, and 15 were rejected as allegedly anticipated by, or obvious over, Gonzales et al (U.S. Pat. No. 6,025,158). Applicants respectfully traverse this rejection. Applicants maintain that Gonzales et al does not anticipate Applicants' invention.

As the Office correctly notes, Gonzales et al describes a polymer molecule used to link together two antibody fragments (col. 35, lines 40-57). And, Gonzales et al describes the attaching of a polymer to the hinge region of **a** parental antibody fragment (not two antibody fragments), preferably via cysteine residues that have been engineered into the fragment (col. 19, lines 35-55). What Gonzales et al does not describe, however, is a polymer molecule

specifically linking two antibody fragments through a cysteine residue on the heavy chain of each fragment, i.e., the subject matter of claim 1.

> Nor can it be said that Applicants' invention is inherently disclosed by Gonzales et al. To establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference...Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient."

MPEP 2112, IV, citing *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999).

As noted above, Gonzales et al does not disclose a polymer molecule specifically linking two antibody fragments through a cysteine residue on each fragment . Applicants maintain that the missing descriptive matter is not **necessarily** present in Gonzales et al. Indeed, the passage cited by the Office reports that such structures can be prepared using a polymer derivatized with **multiple** functional groups permitting the attachment of two or more antibody fragments to the polymer backbone (See column 35, lines 53-57). The use of multiple functional groups, however, suggests multiple attachment locations, not the same location on each heavy chain, much less a cysteine residue on each heavy chain. Indeed, Gonzales et al lists a variety of crosslinking sites on the antibody fragments that can be used, e.g., N-terminal amino groups and epsilon amino groups found on lysine residues, amino groups, imino groups, carboxyl groups,

sulfhydryl groups, hydroxyl groups, and other hydrophilic groups (See column 41, lines 63-57). While it may be *possible* that two of the multiple groups could react with cysteine residues, the mere possibility of this occurrence is not sufficient for anticipation.

Nor is Applicants' invention obvious over Gonzales et al. There must be some motivation to prepare the invention claimed. There is none. As noted above, even the passage which discusses attaching two antibody fragments to a polymer suggests using **multiple** functional groups, not a single functional group, much less a functional group that reacts with a cysteine.

In fact, viewing the disclosure as a whole would lead one away from Applicants' invention. As argued previously, when Gonzales et al discusses linking a polymer to a cysteine residue in one chain of a divalent antibody fragment, the formation of an interchain bridge with the other chain is specifically avoided by substituting another amino acid for the cysteine on the opposite chain. See, for example, column 23, line 16, through column 25, line 44 and column 31, line 55 through column 34, line 28.

Applicants respectfully request that this rejection be withdrawn.

Rejection Under 35 U.S.C. § 103(a)

Claims 1 and 13-14 were again rejected as allegedly unpatentable over Gonzales et al in view of Barbanti et al (5,436,154). Applicants traverse this rejection.

The Office stated that Gonzales et al had been noted for "generically teaching the coupling/bridging of Fab, Fab', or Fab'-SH antibody fragments of generic binding specificity, or

more particularly of IL-8 binding specificity, to a polymer to extend circulating half-life" (Office Action, page 7). As argued above, argument incorporated herein, Gonzales et al does not teach or suggest coupling two antibody fragments to a single polymer through a cysteine residue on a heavy chain of each as claimed. Barbanti et al does not overcome this deficiency.

Further, the Office is inappropriately relying upon what the Office alleges to be the expectation that increasing the circulating half life of **any** antibody to **any** mediator of inflammation would be expected to permit more of the administered antibody to bind to the mediator as support for considering Barbanti et al with Gonzales et al. This analysis, however, puts the cart before the horse. One cannot use a reasonable expectation of success to establish the motivation to combine. MPEP §2143. The Office first needs to show motivation for increasing the circulating half life of any antibody fragment, more specifically, for TNF-α, which it has not done.

Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

Applicants respectfully submit that the above-identified application is now in condition for allowance and request early notification of the same.

Respectfully submitted,

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